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08/359,937	12/20/94	ILLUM	EPC148C1

EXAMINER	ART UNIT	PAPER NUMBER
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DATE MAILED: 04/25/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 1-31-97 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire _____ month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-28 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-28 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

DETAILED ACTION

The requests for the extension of time and reconsideration filed on 1-31-97 are acknowledged.

Claims included in the prosecution are 1-28.

Double Patenting

1. The obviousness type double patenting of claims 1-10 and 15-16 and the non-statutory double patenting of claims 11-14 (now extended to claims 17-28) are maintained in the absence of a terminal disclaimer.

Applicants' arguments that there is nothing in the disclosure of 5,204,108 to suggest instant sizes. This argument is not found to be persuasive. Claim 1 in said patent is a generic claim and does not recite any sizes and thus, it includes micro spheres of instant sizes. With regard to applicants' arguments that in 108 there is no absorption enhancer, the examiner points out that instant claim 1 does not recite absorption enhancer and claim 7 recites the absorption enhancer, but no amounts. Claim 1 of 108 recites, 'substantially free of absorption enhancer' meaning that some enhancer could be present and thus, claim 1 of 108 encompasses even instant claim 7. Applicants' arguments that the method and system are not obvious over the claims in claims in the prior patent are not found to be

persuasive since the this rejection is based on the full disclosure of the prior patent as set forth in the previous action.

The amendment to the independent claims will not overcome the rejection because what is introduced is an intended use and furthermore, applicants have not conclusively established that the cromoglycate administered by the same way in Illum does not enter circulation and thus provide a systemic effect.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 1-6, 11-13 and 16 are rejected under 35 U.S.C. § 103 as being unpatentable over Illum (4,847,091)

Illum, as pointed out before teaches the same micro spheres of instant for nasal inhalation (note the abstract, columns 1-3, examples and claims). Illum however, teaches the composition for only one drug, sodium cromoglycate. Although Illum's compositions are meant for the nasal tissue, it would be obvious to an artisan that systemic absorption of a drug when applied topically is dependent on the nature of the drug and thus, would be motivated to use the micro spheres of Illum with other drugs, if the use of use of micro spheres for systemic use is desired.

3. Claims 1-28 are rejected under 35 U.S.C. § 103 as being unpatentable over Illum (4,847,091) in view of Illum WO 88/09163 of record.

Illum (4,847,091) has been discussed above. As pointed out, Illum does not teach the use of micro spheres for the administration of insulin and other polypeptide drugs. Illum also does not teach the inclusion of penetration enhancers.

Illum in WO teaches micro spheres containing insulin and penetration enhancers (note the abstract, pages 7 -13 and claims).

The use of the micro spheres of Illum 091 for the delivery of insulin and other polypeptide drugs for the systemic delivery would have been obvious to one of ordinary skill in the art with the expectation of obtaining similar absorption since Illum WO teach the use of the micro spheres for such a delivery; the use of penetration enhancers would have been obvious to an artisan since according Illum WO, these enhance the absorption of insulin and other drugs.

4. Claims 1-28 for reasons of record, remain rejected under 35 U.S.C. § 103 as being unpatentable over Illum (1986).

Illum (1986) discloses albumin and starch micro spheres which could be used to deliver drugs including peptides and proteins to the nasal mucosa. Illum further discloses that the micro spheres could be modified by cross-linking (note the discussion section on page 207). According to Illum, such a system would ensure an increased time of contact between the delivery system and the mucosa by a process of bioadhesion with the

possibility of additionally releasing the drug from the system in a sustained and controlled manner (note page 206). The important factors including the particle sizes are also disclosed by Illum (pages 206-207). Pump spray is disclosed on page 208.

Although Illum's teachings do not include the use of penetration enhancers, her disclosure includes the knowledge in the art of the use of such enhancers for nasal (mucosal) delivery of proteins (see 3rd paragraph, Introduction). Instant invention thus, is deemed to be an obvious extension of Illum.

5. Claims 1-28 for reasons of record, are rejected under 35 U.S.C. § 103 as being unpatentable over Illum (4,847,091) in view of Hanson et al or Salzman et al or vice versa.

Illum, 091 has been discussed above. What is lacking in these publications is the teaching of the use of the micro spheres with polypeptide drugs such as insulin. What is also lacking is the teaching of the use of absorption enhancers.

Hansen et al disclose that biological response to nasal administration of calcitonin could be increased by the inclusion of various surfactants ion the formulation (see the conclusion on page 241). Hansen et al's disclosure does not include the use of micro spheres.

Salzman et al disclose that intranasal administration of insulin in combination with a non-ionic detergent increases the absorption of insulin (note discussion on page 1081).

To use the micro spheres of Illum 091 for the delivery of insulin and other polypeptide drugs would have been obvious to an artisan since Hansen and Salzman teach

that insulin could be administered nasally for systemic effect and an artisan would expect at least similar absorption of insulin. To include penetration enhancers such as surfactants taught by Hansen et al or Salzman et al in the micro spheres of Illum would have been obvious to one of ordinary skill in the art since such an inclusion would certainly increase the absorption of drugs from the mucosal membranes.

Alternately, to use the micro spheres of starch or similar swellable and bioadhesive material as taught by Illum in the teachings of Hansen or Salzman would have been obvious to an artisan since such spheres adhere to the nasal tissue and allow the drug to be released in a sustained manner.

6. Claims 7-12, 14, 23-26 for reasons of record, are rejected under 35 U.S.C. § 103 as being unpatentable over Illum (1986) in view of Hanson et al or Salzman et al or vice versa.

Illum 1986 has been discussed before. What is lacking in Illum is the teachings of penetration enhancers. Hansen and Salzman have been discussed above.

To include penetration enhancers such as surfactants taught by Hansen et al or Salzman et al in the micro spheres of Illum would have been obvious to one of ordinary skill in the art since such an inclusion would certainly increase the absorption of drugs from the mucosal membranes.

Alternately, to use the micro spheres of starch or similar swellable and bioadhesive material as taught by Illum in the teachings of Hansen or Salzman would have been

obvious to an artisan since such spheres adhere to the nasal tissue and allow the drug to be released in a sustained manner.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants argue that Illum's (091) micro spheres contain sodium cromoglycate and are for localized treatment and not for systemic treatment. First of all, instant claims recite generic 'drug' and sodium cromoglycate is a drug. Secondly, the intended use has no significance in composition claims. Thirdly, applicants have not demonstrated that the intra nasally applied sodium cromoglycate does not enter into circulation at all. Applicants argue that in the supplemental action evidence was submitted to show that sodium cromoglycate is poorly absorbed from the gastrointestinal tract. This argument is not pertinent since instant claims recite nasal delivery and not oral delivery and the prior art teaches nasal delivery; thus, gastrointestinal system does not play a role at all. Applicants argue that Illum (1986) does not teach particles of sizes less than 20 micrometers and in fact Illum teaches away by suggesting the use of particles of sizes 40-60 microns. The examiner disagrees and points out that the sizes of 40-60 refers to the swelled sizes and instant claims do not recite swelled sizes of less than 10 microns. Illum's particles are intended to deliver therapeutic drugs such as insulin; insulin is known to be used of diabetes and it would thus, be obvious to an artisan that Illum teaches intranasal delivery intended of systemic effect. With regard to unexpected results argued by applicants, as pointed out above, the sizes of 40-60 in Illum are swelled sizes and for a proper comparison showing unexpected results, a

comparison must made with the unswelled sizes in Illum. Furthermore, significant improvement does not constitute unexpected results, but rather a routine experimentation by an artisan from Illum's suggestions regarding sizes on page 209, last four lines.

Applicants argue that nothing in Hanson or Salzman teaches or suggests the claimed formulation of micro spheres of instant sizes. The examiner points out that these references were combined with the primary references to show the motivation for one of ordinary skill in the art to use surfactants; applicants provide no specific arguments regarding surfactant effect taught by these references.

1. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *G.S. Kishore* whose telephone number is (703) 308-2440.

The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T.K. Page, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-5408.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-2351.

G S Kishore

Gollamudi S. Kishore, PhD
Primary Examiner
Group 1500

gsk

April 24, 1997